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Title : SYNTHESIS OF 3,4-FUSED γ-LACTONE-γ-LACTAM AND γ-LACTONE-PYRROLIDINE BICYCLIC SYSTEMS

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In this study, bicyclic moieties 3,4-fused γ-lactone-γ-lactam and γ-lactone-pyrrolidine were chosen as the target molecules due to their highly functionalized structures and their ability to be bioactive 5,5-bicyclic molecules. The synthetic strategy was divided into three main parts in which the first part concentrated on the construction of the key-intermediates, lactam and pyrrolidine ring moieties, from D-alanine methyl ester hydrochloride. The approach involved N-protection of the starting material with either benzyl or Boc protecting groups. Condensation with methyl malonyl chloride followed by Dieckmann cyclization gave the required γ-lactam ring moiety 5 which is also known as the β,β-diketoester with an overall yield of 39%. Consequently, decarboxylation of the methyl ester functional group followed by reduction of the keto amide functionality with LiAlH4 afforded the desired pyrrolidine ring 25 in 18% overall yield. The second part focused on the formation of the fused γ-lactone-γ-lactam and γ-lactone-pyrrolidine bicyclic systems. The γ-lactam ring moiety underwent C-alkylation reaction at the C3-position via insertion of the ethyl acetyl functionality by utilizing TBAF as the base. Subsequently, selective dimethoxy-carbonylation was performed using two different decarboxylating agents which were a salt-solvent system, LiI/DMF, and an acid medium, HCl/AcOH; both successfully gave decarboxylated products but the former with the presence of C-3 methyl group as anticipated and the latter without. Accordingly, reduction of the C-4 carbonyl keto of the γ-lactam rings with NaBH4 in acid-base condition had concomitantly lactonized the systems to furnish the desired 3,4-fused γ-lactone-γ-lactam synthons 1 and 8 in 4% and 2% overall yields, respectively, in diastereomeric mixtures. Alternatively, prior to the concurrent lactonization, the γ-lactam rings with C-3 ester functionality were also hydrolysed into their respective carboxylic acid-lactam analogues with LiOH. These leading compounds were then further explored to furnish the desired bicyclic systems via different lactonization procedures. The final part of this study emphasizes on various lactonization protocols through carboxylic acid activation modes using four different reagents which were p-toluenesulfonyl chloride, carbodiimides, cyanuric chloride and phosphorus-based reagent. Final transformations of the γ-lactone-γ-lactam systems into 5,5-bicyclic derivatives were carried out through direct aldol reactions with five different aldehydes which include benzaldehyde, 4-nitrobenzaldehyde, 4-methoxybenzaldehyde, isobutyraldehyde and acetaldehyde. In conclusion, not only 15 new bicyclic-aldol derivatives were successfully synthesized, but various synthetic approaches and most importantly different lactonization procedures were also explored towards the formation of the target fused ring systems. The structures of all synthesized compounds and intermediates were characterized using spectroscopic techniques. The presence and ratio of some diastereomers were analysed using chiral HPLC.